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Genome

Structure

PopSet

Taxonomy

OMIM

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Limits

Preview/Index

History

Go

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Clipboard

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Display

Abstract

Save

Text

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Entrez PubMed

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Help | FAQ

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New/Noteworthy

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MeSH Browser

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Batch Citation Matcher

Clinical Queries

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 1: Gene Ther 1994 May;1(3):170-5

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Gene therapy for cancer using tumour-specific prodrug activation.**Harris JD, Gutierrez AA, Hurst HC, Sikora K, Lemoine NR.**

Imperial Cancer Research Fund Oncology Unit, Royal Postgraduate Medical School, Hammersmith Hospital, London, UK.

Current treatments for metastatic malignant disease are often ineffective. One of the most promising of the selective genetic strategies against cancer is VDEPT (virally directed enzyme prodrug therapy). This uses a viral vector to carry a prodrug-activating enzyme gene into both tumour and normal cells. By linking the foreign gene downstream of tumour-specific transcription units, tumour-specific expression of the foreign enzyme gene can be achieved. We have developed a genetic therapy strategy using VDEPT against cancers that overexpress the oncogene ERBB2. This occurs in approximately one-third of breast and pancreatic tumours (and in a smaller proportion of other tumours) and involves transcriptional up-regulation of the ERBB2 gene with or without gene amplification. We have constructed a chimeric minigene consisting of the proximal ERBB2 promoter linked to the gene encoding cytosine deaminase, an enzyme that can deaminate the prodrug 5-fluorocytosine (5-FC) to form cytotoxic 5-fluorouracil (5-FU). We have constructed a double-copy recombinant retrovirus to deliver the enzyme gene under the control of the ERBB2 promoter into a panel of ERBB2 expression-positive (ERBB2+) and -negative (ERBB2-) pancreatic and breast cell lines. Cytosine deaminase activity was high in ERBB2+ transduced cells but was not detected in ERBB2- transduced cells. Significant cell death was observed in ERBB2+ transduced cells treated with 5-FC whereas ERBB2- cells were not affected. Hence we present a novel gene therapy strategy that is potentially tumour-specific and could be used against a range of tumour types that overexpress the ERBB2 oncogene.

PMID: 7584078 [PubMed - indexed for MEDLINE]